UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,448	10/27/2003	Kathleen C.M. Campbell	SIU 7398	8896

321 7590 09/10/2007

SENNIGER POWERS
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS, MO 63102

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
09/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspatents@senniger.com

Office Action Summary	Application No.	Applicant(s)	
	10/694,448	CAMPBELL, KATHLEEN C.M.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS,. WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007 and 01 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-33,35,36 and 38-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-33,35,36 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1, 3-5, 7-33, 35-36, & 38-45 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 4/19/2007 and Information Disclosure Statement filed 5/1/2007 have been received and entered into the application. Accordingly, claims 1, 3, 33, and 35 have been amended. Also, as reflected by the attached, completed copy of USPTO Form 1449 the cited references have been considered.

In view of the above amendments, the following rejections have been overcome and thus are *withdrawn*:

i) 35 U.S.C. § 102(b) rejection of claims 1, 3-4, 8, 17-25, 30-33, and 35-36; and

ii) 35 U.S.C. § 103(a) rejection of claims 1, 3-5, 7-33, 35-36, and 38-45.

The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-33, 35-36, and 38-45 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for reducing the incidence of ototoxicity in a patient undergoing treatment with CDDP, does not reasonably provide enablement for preventing ototoxicity in a patient undergoing treatment with CDDP or for reducing the incidence of ototoxicity in patients undergoing treatment with other platinum-coordinating compounds or aminoglycoside antibiotics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to preventing or reducing the incidence of ototoxicity in a human, cat, or dog undergoing treatment with a platinum-coordination compound or an aminoglycoside antibiotic comprising administering methionine.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

In the instant case, the term "preventing" is an absolute term meaning that a patient will never develop ototoxicity, of any degree, if they are administered methionine. Such prevention of ototoxicity has never been established in the prior art. In fact, Applicant teaches that patients undergoing treatment with platinum-coordination compounds often experience "delayed toxic effects" (page 44, lines 1-12). Further, ototoxicity is defined in the specification to include "any

detrimental or pathologic change in the structure or function of the ear", including changes in hearing and balance, tinnitus, vertigo, nausea, vomiting, dizziness, and lightheadedness (page 25, line 14 to page 26, line 5). Accordingly, to enable the prevention of "ototoxicity" requires more than a showing that methionine is an effective treatment. It is simply beyond the scope of the present invention to prevent such symptoms as tinnitus, vertigo, nausea, vomiting, and dizziness.

Further, it is not predictable that a compound (D-methionine), which protects rats undergoing treatment with CDDP against some symptoms of ototoxicity, would also effectively treat animals undergoing treatment with other platinum-coordinating compounds or aminoglycoside antibiotics. The mechanism through which D-methionine exerts its protective effect against CDDP ototoxicity appears to be through its binding to CDDP. Whether methionine will bind to other platinum-coordinating compounds or aminoglycoside antibiotics and protect against ototoxicity is not known or predictable based on Applicant's disclosure. In fact, as Applicant states at page 8, lines 19-23, "[T]he foregoing discussion demonstrates that it is not possible to predict reliably which particular sulfur-containing nucleophile will exhibit a platinum-containing compound protective effect in any particular cell, tissue, or organ".

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting preventing or reducing the incidence of ototoxicity in any patient undergoing treatment with a platinum-coordination compound by administering methionine. Others, such as claims 15-17, are narrower, reciting specific species of platinum-coordinating compounds. Still others recite

preventing or reducing the incidence of ototoxicity in any patient undergoing treatment with an aminoglycoside antibiotic by administering methionine. All, however, are extremely broad insofar as they disclose the absolute prevention of ototoxicity, including all symptoms thereof, by administering methionine.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to prevent ototoxicity, particularly in humans. The only working example is limited to administration of a single isomer of methionine (D-methionine) to rats undergoing treatment with a single specie of platinum-coordinating compound (CDDP). However, in this study it is not apparent that all symptoms of "ototoxicity" were monitored. As such, it is not seen how the methods described in the specification could be used to test the claimed compounds for absolute prevention of any and all ototoxicity. Further, only D-methionine was tested in rats being treated with CDDP. Such a test does not reasonably correlate to the prevention or treatment of ototoxicity in humans, cats, and dogs undergoing treatment with any and all platinum-coordination compounds or aminoglycoside antibiotics. For example, D-methionine is known to bind to CDDP and thus may be the mechanism through with D-methionine exerts its protective effects. However, whether such protection will be afforded in patients undergoing treatment with other platinum-coordinating compounds or aminoglycoside antibiotics requires further experimentation.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that methionine could be predictably used as a prevention for ototoxicity in patients undergoing treatment with all platinum-coordinating compounds and aminoglycoside antibiotics as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicant has presented a general idea that because D-methionine offered protection against some symptoms of ototoxicity in rats being treated with CDDP, methionine must therefore, *a priori*, be useful in the prevention of ototoxicity in humans, cats, and dogs undergoing treatment with any platinum-coordinating compound or aminoglycoside antibiotic. However, given that the mechanism through which D-methionine exerts its protective effects is likely through binding to CDDP, it is not seen that ototoxicity resulting from treatment with structurally diverse platinum-coordinating compounds or aminoglycoside antibiotics could predictably be treated with other methionine isomers.

Determining if any particular methionine isomer or combination thereof would treat or prevent ototoxicity resulting from the administration of any platinum-coordinating compound or aminoglycoside antibiotic would require formulation into a suitable dosage forms and subjecting

them to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by the Applicant. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 1, 3-5, 7-14, 18-33, 35-36, and 38-45 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

In the instant case, the claims recite "platinum-coordination compound[s]" and "aminoglycoside antibiotic[s]". Other than those platinum-coordination compounds and aminoglycoside antibiotics explicitly disclosed in the specification, Applicant has provided inadequate written description of the claimed genera.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition,

such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant has failed to provide any structural characteristics, chemical formula, name(s) or physical properties, aside from the express identification of the platinum-coordination compounds named on page 33, lines 7-26 and the aminoglycoside antibiotics named at page 34, line 22 to page 35, line 5, that would provide adequate written description of the genera of compounds encompassed by the claims. As such, it is not evident that Applicant was actually in possession of, and intended to be used within the context of the present invention, the broad genera of "platinum-coordinating compound" and "aminoglycoside antibiotic" at the time the invention was made.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 8, 10-17, and 19-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Basinger et al. (Toxicology and Applied Pharmacology, 1990, vol. 108, pages 1-15) (cited by Applicant in IDS filed 2/28/2005).

The instant claims recite methods of preventing or reducing the incidence of ototoxicity in a patient undergoing treatment with a platinum-coordination compound comprising administering methionine.

Basinger *et al.* teach that *cis*-platinum (CDDP) is an effective antitumor compound whose administration leads to does-limiting toxicities such as nephrotoxicity, myelosuppression, gastrointestinal toxicity, nausea, ototoxicity, peripheral neuropathies, and anaphylactic reactions (page 1, left column). Comprehensive studies of thiols and thioethers provide evidence that such compounds provide renal protection without altering the antineoplastic activity of CDDP (page 2, left column). In this regard, D-methionine, L-methionine, and some of their derivatives were the most effective agents studied (*id.*). In the present study, the authors examined the effects of L-methionine on CDDP nephrotoxicity in rats to determine the degree of renal protection obtained when the ratio of L-methionine to CDDP was varied (*id.*). Thus, CDDP and methionine were simultaneously administered to rats bearing Walker 256 carcinomas. Such administration renders obvious the combined simultaneous *i.v.* administration of a platinum-coordinating compound and methionine as recited in instant claims 1, 3-5, 8, and 10-17. A 20:1 molar excess

of L-methionine to CDDP was simultaneously administered to Sprague-Dawley rats (page 2, right column). This ratio renders obvious the ratios recited in instant claims 23-26. With respect to the dosage of L-methionine recited in instant claims 19-22 and 31-32, Basinger *et al.* teach the administration of varying mole ratios of methionine to CDDP wherein the CDDP is administered in doses of 7.5 mg/kg to 56 mg/kg. The authors conclude that the results obtained clearly indicate that the co-administration of L-methionine and CDDP results in a very significant decrease in the nephrotoxicity found with the CDDP alone and that such treatment results in antitumor activity (page 9, right column).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art:

In the instant case, Basinger *et al.* teach that co-administration of L-methionine and CDDP to rats having Walker 256 carcinomas results in both antitumor activity and reduced nephrotoxicity. The doses administered are within the instantly claimed dose ranges and ratios.

Differences Between Prior Art and Claims:

The administration of L-methionine and CDDP to rats as taught in Basinger *et al.* differs from the instant claims in two ways. Firstly, the instant claims recite administration to humans, cats, or dogs. Basinger *et al.* teach administration to rats, a common preclinical animal model. Secondly, the instant claims recite a method of preventing or reducing ototoxicity resulting from administration of a platinum-coordinating compound such as CDDP. Basinger *et al.* only evaluated the effect of the combined therapy on nephrotoxicity, although they do teach that ototoxicity is a known side effect of CDDP therapy.

Level of Ordinary Skill in the Art:

A person having ordinary skill in the art at the time of the present invention would generally be a physician or pharmacologist having several years of experience in drug administration and toxic effects thereof.

Objective Evidence and Motivation:

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to administer methionine in combination with CDDP to other mammals in order to reduce the nephrotoxicity caused by CDDP treatment. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)). In this case, Basinger *et al.* explicitly teach that the claimed compound

is effective in reducing nephrotoxicity associated with CDDP therapy in rats. As such, testing the combined therapy in other animal models would be the next logical step.

With respect to the instantly claimed effect of such combined therapy (reducing ototoxicity), CDDP therapy is known in the art to result in ototoxicity. As such, administration of methionine to animals receiving CDDP will naturally result in the claimed effect because a compound or composition and its properties are not separable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In this case, a composition comprising CDDP and methionine administered to a patient undergoing CDDP therapy will result in a reduction of ototoxicity. The fact that Basinger *et al.* did not monitor the animals for such an effect is not pertinent to the present rejection. The motivation to co-administer methionine and CDDP to animals undergoing CDDP therapy is explicitly found in the prior art – such co-administration results in decreased nephrotoxicity. There may very well be other beneficial effects of such treatment (as Applicant is now claiming), but the Examiner questions how the patient population being instantly treated differs from a patient population generally being administered CDDP. Nephrotoxicity, ototoxicity, myelosuppression, gastrointestinal toxicity, nausea, etc. are all side effects of CDDP therapy as evidenced in Basinger *et al.* Thus, if one skilled in the art is motivated to administer methionine to patients receiving CDDP in order to decrease nephrotoxicity, any other beneficial (or for that matter, detrimental) effects of such treatment will naturally result.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to administer a combination of methionine and CDDP to patients undergoing CDDP therapy. This

is especially true given that methionine has been demonstrated to lessen the nephrotoxicity associated with treatment with CDDP. Accordingly, in the absence of a showing that a patient undergoing therapy with CDDP and developing nephrotoxicity is distinct from a patient undergoing therapy with CDDP and developing ototoxicity, the claimed methods would have been *prima facie* obvious. As noted *supra*, the effects of administering methionine and CDDP to a patient are not separable from the composition if the composition is being administered to the same patient population.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

August 29, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER